

that expresses a wild-type patched protein and identifying one or more test agents that decrease the level of hedgehog signal transduction relative to the absence of test agent, wherein an agent that decreases hedgehog signal transduction is useful for ameliorating an affect in a mammalian cell characterized by loss of function of a patched gene.

62. **(Five Times Amended)** A method for identifying an agent for ameliorating an affect of loss of function of a patched gene in a mammalian cell, comprising contacting one or more test agents with a mammalian cell in culture characterized by loss of function of a patched gene and identifying one or more test agents that increase patched activity relative to the absence of test agent, wherein an agent that increases patched activity is useful for ameliorating an affect in a mammalian cell characterized by loss of function of a patched gene.

63. **(Five Times Amended)** A method for identifying an agent which increases patched activity in a mammalian cell characterized by loss of function of a patched gene, comprising:

a. comparing the amount of expression of a reporter gene in a recombinant mammalian cell in culture in the presence of a test agent with the amount of expression in the absence of the agent; and

b. identifying test agents that decrease the amount of expression of the reporter gene in the recombinant cell in the presence of the agent compared to the amount of expression in the absence of the agent, wherein:

the recombinant cell contains a reporter gene construct and said recombinant cell does not express a functional wild-type patched protein; and

the reporter gene construct contains:

(i) a transcriptional control element that is stimulated by hedgehog signal transduction; and

(ii) a reporter gene that encodes a detectable product and that is in operative association with the transcriptional control element;

wherein a test agent identified in step (b) increases patched activity in a mammalian cell characterized by loss of function of a patched gene.

64 **(Reiterated)** The method of claim 63, wherein the amount of transcription is determined by measuring the amount of mRNA that is transcribed from said reporter gene.

65. **(Reiterated)** The method of claim 63, wherein the amount of transcription is measured by measuring the amount of a reporter gene protein that is produced.
66. **(Reiterated)** The method of claim 63, further comprising, prior to comparing the difference in the amount of transcription of the reporter gene, contacting the recombinant cell with a hedgehog agonist in an amount sufficient to change the level of transcription of said reporter gene.
67. **(Reiterated)** The method of claim 63, wherein the reporter gene is at least one of a gene encoding chloramphenicol acetyltransferase, a gene encoding firefly luciferase, a gene encoding bacterial luciferase, or a gene encoding alkaline phosphatase.
68. **(Reiterated)** The method of claim 63, wherein the transcriptional control region includes at least one regulatory element selected from transcriptional regulatory elements of a patched gene, transcriptional regulatory elements of a gli gene, or transcriptional regulatory elements of a PTHrP gene.
70. **(Reiterated)** The method of claim 63, wherein expression of the reporter gene occurs upon hedgehog stimulation, and compounds are selected by ability to inhibit the expression of the reporter gene.
71. **(Reiterated)** The method of claim 63, wherein the cell characterized by a loss of function of a patched gene is a basal cell carcinoma cell.
74. **(Reiterated)** The method of claim 61 or 62, further comprising preparing a formulation including an agent which decreases hedgehog signal transduction and a pharmaceutically acceptable excipient.
75. **(Reiterated)** The method of claim 74, further comprising administering the formulation to a patient.

76. **(Reiterated)** The method of claim 63, further comprising preparing a formulation including an agent which decreases hedgehog signal transduction and a pharmaceutically acceptable excipient.

77. **(Reiterated)** The method of claim 76, further comprising administering the formulation to a patient.

Please add the following new claims:

78. **(NEW)** A method for identifying an agent which increases patched activity in a cell characterized by loss of function of a patched gene, comprising:

- a. comparing the amount of mRNA transcribed from a reporter gene in a recombinant mammalian cell in the presence of a test agent with the amount of mRNA transcribed from a reporter gene in the absence of the agent; and
- b. identifying test agents that decrease the amount of mRNA transcribed from the reporter gene in the recombinant cell in the presence of the agent compared to the amount of mRNA transcribed from the reporter gene in the absence of the agent, wherein:

the recombinant cell contains a reporter gene construct and said recombinant cell does not express a functional wild-type patched protein; and

the reporter gene construct contains:

- (i) a transcriptional control element that is stimulated by hedgehog signal transduction; and
- (ii) a reporter gene that encodes a detectable product and that is in operative association with the transcriptional control element;

wherein a test agent identified in step (b) increases patched activity in a mammalian cell characterized by loss of function of a patched gene.

79. **(NEW)** A method for identifying an agent which increases patched activity in a mammalian cell characterized by loss of function of a patched gene, comprising:

- a. comparing the amount of expression of a reporter gene in a recombinant mammalian cell in the presence of a test agent with the amount of expression in the absence of the agent; and

b. identifying test agents that decrease the amount of expression of the reporter gene in the recombinant cell in the presence of the agent compared to the amount of expression in the absence of the agent, wherein:

the recombinant cell contains a reporter gene construct selected from a gene encoding chloramphenicol acetyltransferase, a gene encoding firefly luciferase, a gene encoding bacterial luciferase, or a gene encoding alkaline phosphatase, and said recombinant cell does not express a functional wild-type patched protein; and

the reporter gene construct contains:

- (i) a transcriptional control element that is stimulated by hedgehog signal transduction; and
- (ii) a reporter gene that encodes a detectable product and that is in operative association with the transcriptional control element;

wherein a test agent identified in step (b) increases patched activity in a mammalian cell characterized by loss of function of a patched gene.

80. (NEW) A method for identifying an agent which increases patched activity in a mammalian cell characterized by loss of function of a patched gene, comprising:

a. comparing the amount of expression of a reporter gene in a recombinant mammalian cell in the presence of a test agent with the amount of expression in the absence of the agent; and

b. identifying test agents that decrease the amount of expression of the reporter gene in the recombinant cell in the presence of the agent compared to the amount of expression in the absence of the agent, wherein:

the recombinant cell contains a reporter gene construct and said recombinant cell is a basal cell carcinoma cell that does not express a functional wild-type patched protein; and

the reporter gene construct contains:

- (i) a transcriptional control element that is stimulated by hedgehog signal transduction; and
- (ii) a reporter gene that encodes a detectable product and that is in operative association with the transcriptional control element;

wherein a test agent identified in step (b) increases patched activity in a mammalian cell characterized by loss of function of a patched gene.

81. (NEW) A method for preparing an agent for inhibiting growth of cells characterized by loss of function of a patched gene, comprising:

- a. contacting one or more test agents with a mammalian cell that expresses a wild-type patched protein and identifying test agents that decrease the level of hedgehog signal transduction relative to the absence of test agent;
- b. contacting test agents identified in step (a) with a mammalian cell having a loss of function of a patched gene, wherein said cell is a basal cell carcinoma cell, and selecting those test agents that inhibit growth of mammalian cells having a loss of function of a patched gene; and
- c. preparing a formulation including a test agent that inhibits the growth of mammalian cells selected in step (b) and a pharmaceutically acceptable diluent.

*The amended claims are re-stated below to reflect changes from the last filing.*

61. (Five Times Amended) A method for identifying an agent which decreases hedgehog signal transduction for ameliorating an affect of loss of function of a patched gene in a mammalian cell, comprising contacting one or more test agents with a mammalian cell in culture that expresses a wild-type patched protein and identifying one or more test agents that decrease the level of hedgehog signal transduction relative to the absence of test agent, wherein an agent that decreases hedgehog signal transduction is useful for ameliorating an affect in a mammalian cell characterized by loss of function of a patched gene.

62. (Five Times Amended) A method for identifying an agent ~~which decreases hedgehog signal transduction~~ for ameliorating an affect of loss of function of a patched gene in a mammalian cell, comprising contacting one or more test agents with a mammalian cell in culture characterized by loss of function of a patched gene and identifying one or more test agents that increase patched activity ~~decrease the level of hedgehog signal transduction~~ relative to the

absence of test agent, wherein an agent that increases patched activity ~~decreases hedgehog signal transduction~~ is useful for ameliorating an affect in a mammalian cell characterized by loss of function of a patched gene.

63. **(Five Times Amended)** A method for identifying an agent which increases patched activity ~~decreases hedgehog signal transduction~~ in a mammalian cell characterized by loss of function of a patched gene, comprising:

- a. comparing the amount of expression of a reporter gene in a recombinant mammalian cell in culture in the presence of a test agent with the amount of expression in the absence of the agent; and
- b. identifying test agents that decrease the amount of expression of the reporter gene in the recombinant cell in the presence of the agent compared to the amount of expression in the absence of the agent, wherein:

the recombinant cell contains a reporter gene construct and said recombinant cell does not express a functional wild-type patched protein; and

the reporter gene construct contains:

- (i) a transcriptional control element that is stimulated by hedgehog signal transduction; and
- (ii) a reporter gene that encodes a detectable product and that is in operative association with the transcriptional control element;

wherein a test agent identified in step (b) ~~decreases hedgehog signal transduction~~ increases patched activity in a mammalian cell characterized by loss of function of a patched gene.

### REMARKS

Claims 61-77 constitute the pending claims in the present application. Applicants hereby cancel, without prejudice, claims 72 and 73. Applicants add new claims 78-81. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks.

1. Applicants note with appreciation that the amendments of Paper No. 34 have been entered in full.